Glu230, Leu231, Gln232, Asn240, Val241, Thr242, Asp243, Ser245, Val247, Ser248, His249, Gly250, Thr251, Gly252 and Phe253, which correspond to residues 12, 13, 14, 15, 16, 20, 21, 26, 27, 28, 29, 30, 31, 63, 65, 70, 71, 72, 73, 75, 76, 77, 82, 83, 84, 85, 86, 87, 88, 89, 92, 94, 96, 102, 103, 104, 105, 115, 116, 117, 125, 126, 127, 128, 130, 132, 133, 134, 135, 136, 137, and 138, respectively, of SEQ ID NO: 3, according to Table 1; and

b) a computer screen for displaying said three dimensional representation.

C3

REMARKS

Applicants acknowledge, with appreciation, the courtesy extended to their representatives by the Examiner during a telephone interview on March 18, 2002. Applicants make that interview of record herein. Applicants also acknowledge the Examiner's withdrawal of finality of the April 10, 2001 Office Action.

Applicants request reconsideration of the above-identified application in view of the foregoing amendments and the following remarks.

Claims 12, 39, 41 and 42 were pending in the present application at the time of the Office Action. Applicants have canceled claims 12 and 41, without prejudice. Applicants have amended claims 39 and 42 and

have added claim 43 to more particularly point out and distinctly claim the invention. Amended claims 39 and 42 are supported on page 8, lines 1-9 and page 26, lines 15-17 of the specification. Added claim 43 is also supported in the specification. See, e.g., page 20, lines 2-13. These amendments and additions do not constitute new matter.

I. Abstract

The Abstract stands objected to because it is more than one paragraph in length. Applicants have amended the Abstract accordingly. The amended Abstract is one paragraph in length and does not add new matter. See e.g., the former Abstract. See also, claims 12, 39 and 41-42. See also page 8, lines 1-7; page 38, lines 17-18; page 19, line 26 to page 21, line 33; page 1, lines 3-4 and Table 1. Hence, the objection to the Abstract is overcome.

II. Claim Rejections under 35 U.S.C. § 101

Claims 12, 39 and 41-42 stand rejected under 35 U.S.C. § 101 because the claimed invention is purportedly directed to non-statutory matter.

The Examiner states that "claims 12 and 41 are directed to a computer readable medium encoded with data

comprising structure coordinates for amino acids in a CD40 ligand (CD40L)". The Examiner asserts that "structure coordinates are nonfunctional descriptive material as they do not impart any functionality to the computer readable medium nor do they display any functional relationship with a computing process". The Examiner further asserts that "merely storing nonfunctional descriptive material on a computer-readable medium does not render the claimed invention statutory" according to MPEP 2106.II.A and MPEP 2106.IV.B(1). The Examiner also refers to the definition of "nonfunctional descriptive material" in MPEP 2106.IV.B(1).

Applicants have canceled claims 12 and 41, without prejudice. The rejection of those two claims is therefore moot.

The Examiner contends that claims 39 and 42 are purported to recite a machine comprising a computer readable medium similar to that of claims 12 and 41. More specifically, the Examiner contends that "the machine is merely a 'carrier' for nonfunctional descriptive material" since "no structural/physical limitations are recited for the machine". The Examiner further asserts that "structural coordinates recited in claims do not impart functionality to the machine nor do they enter into any interfunctional relationship to the machine, therefore the

structural coordinates do not provide a practical application for the machine claimed". Applicants traverse these claim rejections based on the foregoing amendments and the following remarks.

Amended claims 39 and 42 and added claim 43 recite a computer. This recitation is supported in the specification. See e.g., page 26, lines 16-17, page 35, lines 29-33 and page 37, line 6. For example, the specification, at lines 29-33 on page 35, states that molecular graphics manipulations were carried out using the program QUANTA (Molecular Simulations, Inc.) on a Silicon Graphics (SGI) Indigo2 computer. One skilled in the art would clearly understand the physical structure, features and components of an SGI Indigo2 computer, one commonly used by those skilled in the art.

The structure coordinates recited in amended claims 39 and 42 and added claim 43 enter into an interfunctional relationship with the computer, such that the computer produces a three dimensional representation of a CD40L binding site for CD40 (amended claim 39 and added claim 43) or a molecular or molecular complex as defined in amended claim 42. Thus, each of amended claims 39 and 42 and added claim 43 recites a computer that produces a three dimensional representation of a particular structure and comprises a computer-readable

storage medium. Those claims also recite the physical structure of the computer (a computer screen).

Computer programs, such as Quanta (page 35, lines 30-32; page 26, line 21), Sybyl (page 26, line 21), DOCK, GRID, XSITE, AUTODOCK, CATALYST, MCSS (page 26, lines 24-30) are listed in the specification to enable one of ordinary skill in the art to use a computer to produce the above-described three dimensional representation and to use that three dimensional representation for drug design.

Applicants believe that the claimed invention is a new and useful machine and directed to statutory material, as required by 35 U.S.C. § 101. Accordingly, amended claims 39 and 42 and added claim 43 comply with 35 U.S.C. § 101.

III. Claim Rejections under 35 U.S.C. § 112, 1st Paragraph

Claims 12, 39 and 41-42 stand rejected under 35 U.S.C. § 112, first paragraph, for purported lack of enablement. The Examiner states that the specification "does not reasonably provide enablement for a machine or medium comprising data for displaying a crystal of any CD40L complex, non-human CD40L ligand, full-length CD40 ligand, mutants or variants of any CD40 ligand, any CD40L

fragment other than residues 116-261". The Examiner asserts that "the instant specification teaches only crystallization of sCD40L", and "it would require undue experimentation for one skilled in the art to make and/or use a computer readable medium or machine comprising crystal coordinates for any protein or portion thereof other than that consisting of amino acids 116-261 of CD40L". Applicants disagree.

Applicants have canceled claims 12 and 41, without prejudice, rendering moot a portion of the § 112 rejection.

Amended claim 39 and added claim 43 recite a computer for producing a three dimensional representation of a binding site of CD40 defined by structure coordinates of specific CD40 ligand ("CD40L") amino acids according to Table 1. Applicants' invention provided, for the first time, a computer that can produce a three dimensional representation of a specific structure: the defined binding site for CD40. See amended claim 39 and added claim 43. Applicants are entitled to a claim scope which encompasses any computer that produces a three dimensional representation of that specific structure, i.e., the binding site for CD40 defined in amended claim 39 and added claim 43.

In the § 112 analysis, it is important to note that amended claim 39 and added claim 43 do not claim crystals of CD40L. Rather, these claims recite a computer for producing a three dimensional representation of a binding site of CD40 defined by structure coordinates of specific CD40L amino acids. Applicants clearly enable a person skilled in the art to make and use such a computer. See, e.g. Table 1; page 26, lines 16-17; page 35, lines 29-33; page 37, line 6; and page 19, line 26 to page 20, line 14 of the specification. Specifically, page 26, lines 16-17 and page 37, line 6, discusses the use of a computer to display a binding site or molecule from the structure coordinates. Page 35, lines 29-33 enables the use of a Silicon Graphics Indigo 2 computer for displaying that binding site or molecule. Table 1 lists the structure coordinates themselves, and page 19, line 26 to page 20, line 14 provides the binding site to be displayed using the computer.

Applicants have deleted the phrase "a molecule or molecular complex" in amended claim 39 because the phrase constitutes redundant language in view of the remainder of the claim. A person skilled in the art would understand that any computer that can produce the three dimensional representation of a molecule or molecular complex of a binding site for CD40, including a molecule

or molecular complex comprising mutants or variants of CD40L, full-length CD40L, or longer fragments of CD40L, would fall within the scope of applicants' invention, as long as the representation contains the CD40L binding site according to amended claim 39 or added claim 43.

The structure coordinates for sCD40L(116-261) represent the domain or the fragment of the CD40L protein that binds CD40. The Examiner asserts that applicants have not enabled the invention for proteins other than the fragment sCD40L (116-261). Applicants disagree.

In general, a domain in structural biology is a compact independently folded unit of structure (L. Stryer, "Biochemistry", 3rd edition, pp. 31-32 (1996)), enclosed at Tab D). Typically, the domain will remain essentially the same in structure. One skilled in the art would appreciate that the structure of a longer fragment of the CD40L protein will in fact include the same sCD40L domain structure linked to other domains or structural segments. Applicants are claiming the structure of a domain whose structure is known (that structure was solved by applicants and disclosed in this application); not unknown structures of other domains.

An analogy to protein sequence may be helpful. If an inventor claims a protein comprising a polypeptide having a sequence from residues 233 to 333 as their

invention, that claim encompasses any protein comprising these residues, including for example, a protein from amino acid residues 1 to 400. Applicants believe that structural biology claims are analogous. In the present invention, a structure of a protein fragment comprising a stably-folded domain from residues 116-261 may be part of a structure of a "longer" fragment of the same protein or the full-length protein. The structure of that domain (amino acid residues 116-261), would be expected to be essentially identical in the short domain fragment (116-261), any longer fragment, and the full-length protein. Computers that produce three dimensional representations of the short domain fragment (116-261), any longer fragment, and the full-length protein therefore fall within the scope of the amended claim 39 and added claim 43. Computers that produce three dimensional representations of variants and mutants of CD40L having the binding site for CD40, as defined in amended claim 39 or added claim 43, also fall within the scope of amended claim 39 or added claim 43 and are enabled by the instant disclosure.

The Examiner asserts that changing crystal conditions may alter the structure of the protein. Applicants disagree. Structural biology relies on the theory that the three dimensional structure of a given

protein domain in general is fairly uniform and reflects the biological state. For example, if the three dimensional structure of a protein domain is solved by both NMR and X-ray crystallography, a skilled artisan would expect the structures to be essentially the same within standard experimental error. Crystallization conditions may change the crystal form (e.g., space group in which it crystallizes), resulting in a different crystal packing that may affect local geometry at the packing interface. However, in general, the domains, or sections of domains, not involved in the packing interfaces should remain essentially the same.

Amended claim 42 recites a computer producing a three dimensional representation of a molecule or molecular complex defined by structure coordinates of the CD40 ligand amino acids according to Table 1. To expedite prosecution, the phrase "at least a portion of" has been deleted from claim 42. Amended claim 42 is clearly enabled. See, e.g. Table 1; page 26, lines 16-17; page 35, lines 29-33; and page 37, line 6 of the specification.

Applicants clearly enable a person skilled in the art to use the computers of amended claims 39 and 42 and added claim 43 without undue experimentation. Each of those claims recites a computer that produces a three dimensional representation of a particular biological

structure (i.e., a binding site for CD40 as recited in claims 39 or 43, and a molecule or molecular complex as recited in claim 42), which was provided, described and enabled, by applicants for the first time in this application.

For all the foregoing reasons, applicants believe that the present claims comply with 35 U.S.C. § 112, first paragraph.

Applicants request that the Examiner consider the foregoing amendments and remarks and pass this application to issue.

Respectfully submitted,

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A-07/C

ABSTRACT

The present invention relates to crystals of fragments of CD40 ligand, specifically, a soluble fragment of CD40 ligand (116-261). The invention relates further to uses of these crystals and the coordinates thereof to design, identify, optimize or characterize chemical entities having properties of interest. The present invention also relates to a machine readable medium comprising a machine readable storage material encoded with machine readable data, wherein said data comprises at least a portion of the structure coordinates of a fragment of CD40 ligand, and wherein said data, when read by an appropriate machine, is capable of displaying a three-dimensional representation of a crystal of a molecule or a molecular complex comprising a fragment of CD40 ligand. The present invention further relates to a machine comprising said medium.

APPENDIX TO ABSTRACT AMENDMENT

The present invention relates to crystals of fragments of CD40 ligand, specifically, a soluble fragment of CD40 ligand (116-261). The invention relates further to uses of these crystals and the coordinates thereof to design, identify, optimize or characterize chemical entities having properties of interest. [

]The present invention also relates to a machine readable medium comprising a machine readable storage material encoded with machine readable data, wherein said data comprises at least a portion of the structure coordinates of a fragment of CD40 ligand, and wherein said data, when read by an appropriate machine, is capable of displaying a three dimensional representation of a crystal of a molecule or a molecular complex comprising a fragment of CD40 ligand. The present invention further relates to a machine comprising said medium.

Appendix to Claim Amendment

39. (Twice Amended) [A machine comprising a machine readable data storage medium comprising a data storage material encoded with machine readable data which, when read by said machine, is capable of displaying] A computer for producing a three dimensional representation of [a crystal of a molecule or molecular complex comprising] a binding site for CD40 defined by structure coordinates of [comprising] CD40 ligand amino acids Lys143, Arg203, Arg207 and Tyr145, which correspond to residues 28, 88, 92 and 30, respectively, of SEQ ID NO: 3, according to Table 1; wherein said [data] computer comprises:

(a) a computer-readable data storage medium comprising a data storage material encoded with computer-readable data, wherein said data comprises the structure coordinates of CD40 ligand amino acids Lys143, Arg203, Arg207 and Tyr145, which correspond to residues 28, 88, 92 and 30, respectively, of SEQ ID NO:3, according to Table 1; and

(b) a computer screen for displaying said three dimensional representation.

42. (Amended) [A machine comprising a machine-readable data storage medium comprising a data

storage material encoded with machine-readable data which, when read by said machine, is capable of displaying] A computer for producing a three dimensional representation of [a crystal of] a molecule or a molecular complex defined by [at least a portion of] the structure coordinates of all the CD40 ligand amino acids [116 to 261] according to Table 1[,]; wherein said [data] computer comprises:

(a) a computer-readable data storage medium comprising a data storage material encoded with computer-readable data, wherein said data comprises [at least a portion of] the structure coordinates of the CD40 ligand amino acids [116 to 261] according to Table 1;

and

(b) a computer screen for displaying said three dimensional representation.

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Four levels of structure are frequently cited in discussions of protein architecture. *Primary structure* is the amino acid sequence and the location of disulfides, if there are any. The primary structure is thus a complete description of the covalent connections of a protein. *Secondary structure* refers to the spatial arrangement of amino acid residues that are near one another in the linear sequence. Some of these steric relationships are of a regular kind, giving rise to a periodic structure. The α helix, β pleated sheet, and collagen helix are elements of secondary structure. *Tertiary structure* refers to the spatial arrangement of amino acid residues that are far apart in the linear sequence. The dividing line between secondary and tertiary structure is a matter of taste. Proteins containing more than one polypeptide chain exhibit an additional level of structural organization. Each polypeptide chain in such a protein is called a subunit. *Quaternary structure* refers to the spatial arrangement of such subunits and the nature of their contacts (Figure 2-40). The constituent chains of a multisubunit protein can be identical or different. For example, immunoglobulin G, the major antibody molecule in plasma, consists of two L chains and two H chains. The spherical shell of tomato bushy stunt virus, a plant pathogen, is formed from 180 identical coat protein molecules. The interfaces between subunits are often functionally significant. For example, in hemoglobin (consisting of four chains), the subunit interfaces participate in transmitting information between binding sites for O_2, CO_2, and H^+. In antibody molecules, the combining site for antigen is formed by segments of two different kinds of chains.

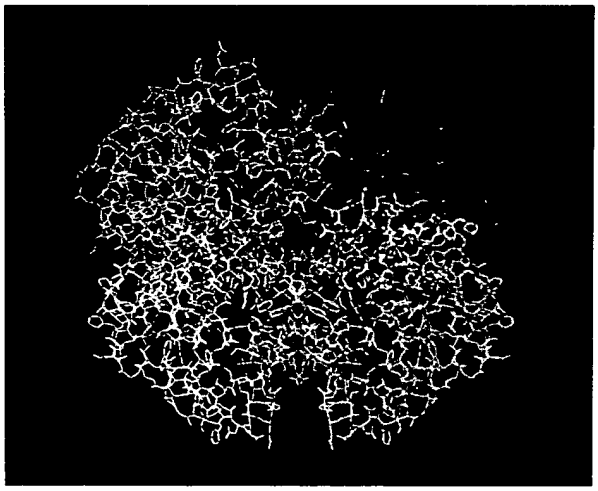


Figure 2-40
Three-dimensional structure of hemoglobin. The four subunits are shown in different colors. Each contains an oxygen-binding heme group (red).

Recent studies of protein conformation, function, and evolution have revealed the importance of two additional levels of organization. *Supersecondary structure* refers to clusters of secondary structure. For example, a β strand separated from another β strand by an α helix is found in many proteins; this motif is called a $\beta\alpha\beta$ unit. It is fruitful to regard supersecondary structures as intermediates between secondary and tertiary structure. Some polypeptide chains fold into two or more compact regions that may be joined by a flexible segment of polypeptide chain, rather like pearls on a string. These compact globular units, called *domains*, range in size from about 100 to 400 amino acid residues. For example, a 25-kd L chain of an antibody is folded into two domains (Figure 2-41). Indeed, these domains resemble one another, which sug-

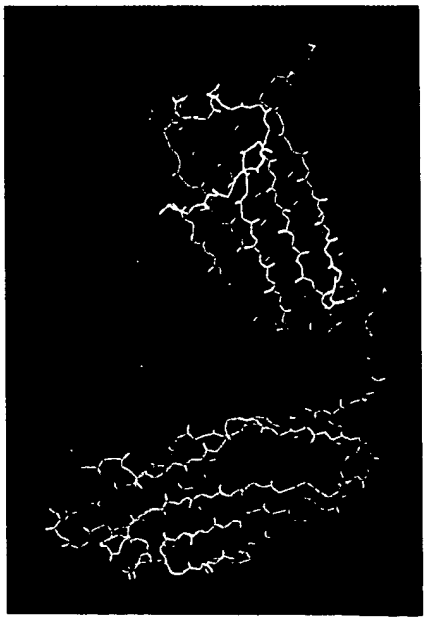


Figure 2-41
The light (L) chain of an antibody molecule consists of two distinct domains.

gests that they arose by duplication of a primordial gene. An important principle has emerged from analyses of genes and proteins in higher eucaryotes: *protein domains are often encoded by distinct parts of genes called exons* (p. 112). In our explorations of genes and proteins, exons and domains will often be at the focal point.

AMINO ACID SEQUENCE SPECIFIES THREE-DIMENSIONAL STRUCTURE

Insight into the relation between the amino acid sequence of a protein and its conformation came from the work of Christian Anfinsen on ribonuclease. As mentioned earlier, ribonuclease is a single polypeptide chain consisting of 124 amino acid residues (Figure 2-42). Its four disul-

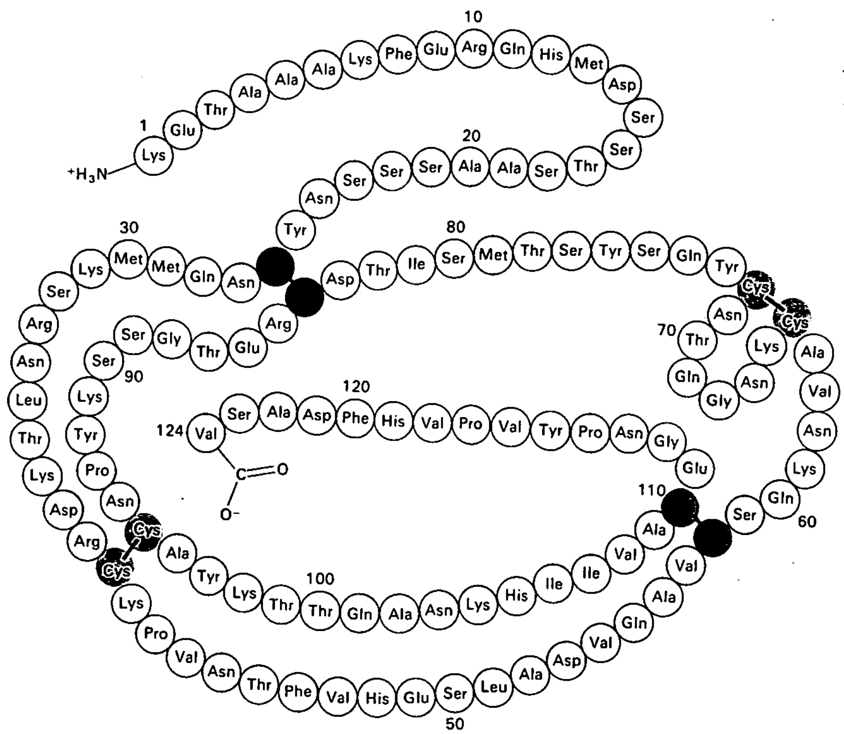
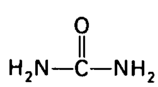
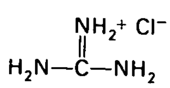


Figure 2-42
Amino acid sequence of bovine ribonuclease. The four disulfide bonds are shown in color. [After C. H. W. Hirs, S. Moore, and W. H. Stein. *J. Biol. Chem.* 235(1960):633.]

fide bonds can be cleaved reversibly by reducing them with a reagent such as *β-mercaptoethanol,* which forms mixed disulfides with cysteine side chains (Figure 2-43). In the presence of a large excess of β-mercaptoethanol, the mixed disulfides also are reduced, so that the final product is a protein in which the disulfides (cystines) are fully converted into sulfhydryls (cysteines). However, it was found that ribonuclease at 37°C and pH 7 cannot be readily reduced by β-mercaptoethanol unless the protein is partly unfolded by agents such as *urea* or *guanidine hydrochloride.* Although the mechanism of action of



Urea



Guanidine hydrochloride

$HO-CH_2-CH_2-SH$

β-Mercaptoethanol

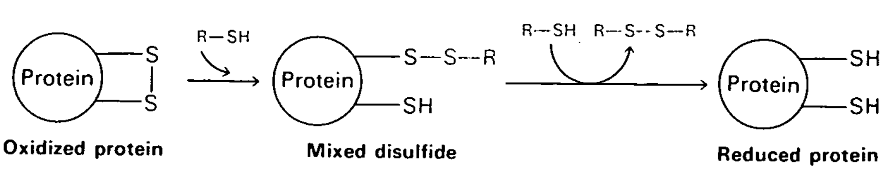


Figure 2-43
Reduction of the disulfide bonds in a protein by an excess of a sulfhydryl reagent such as β-mercaptoethanol.